Review Article

Treatment strategies for locally advanced rectal cancer with synchronous resectable liver metastasis

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Abstract

Approximately one-third of patients with colorectal cancer are estimated to be diagnosed with synchronous liver metastasis (LM). The only method to get cured is to achieve curative resection for both primary and LM. When it comes to locally advanced rectal cancer with synchronous LM, determination of the treatment strategy for each individual is a quite complex procedure, because it demands sophisticated consideration for both local and systemic control. Timing for the application of systemic chemotherapy (CTx), determination of a chemotherapeutic agent, radiation dose and fractions, and sequencing of preoperative treatment and surgeries are all essential components for establishing optimal treatment strategies for the patients with this disease. In this article, treatment strategies proposed in the literature will be reviewed in the light of oncologic outcomes and treatment toxicity with their possible advantages and disadvantages. Owing to a lack of concrete evidences for the best strategy, this article can guide authors to a better way of determining more tailored treatment for each individual.

Keywords: Locally advanced rectal cancer, synchronous liver metastasis, treatment strategy

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INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide. Approximately one-third of patients usually have systemic metastasis at their initial diagnosis.[1] The liver is the most commonly metastasized organ for primary colorectal cancer.[2] Treatment of synchronous liver metastasis (LM) from primary rectal cancer is quite challenging and complicated. Synchronous LM is considered biologically different from metachronous LM due to its poorer oncologic outcomes,[3] and there are several factors that should be carefully decided, such as modalities of preoperative treatment, timing of surgery, systemic chemotherapy (CTx), and their possible sequences considering existence of symptoms caused by primary tumor and respectability of both sites.

Unlike for colon cancer with synchronous LM, a more complex procedure for the determination of the optimal treatment strategies is required for rectal cancer with synchronous LM, especially when a patient presents locally advanced rectal cancer (LARC) [Figure 1]. This is because local treatment with chemoradiation therapy (CRT) is needed and tumor regression of rectal cancer should be considered. Completing preoperative CRT with conventionally fractionated radiotherapy (RT) can lead to delay in the administration of systemic CTx. This can

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cause aggravation of distant metastasis, even if the LM was initially resectable, potentially resulting in loss of opportunity for the patients of R0 resection, which is the only treatment that can achieve complete curability to date. Therefore, the previous studies have proposed treatment strategies to overcome this critical drawback that can occur during treatment for local control.[4-8]

This article will focus on the treatment strategies for the patients presenting LARC with synchronous resectable LM, and theoretical background and clinical outcomes of the treatment strategies proposed in the literature will be reviewed.

DEFINITIONS OF LOCALLY ADVANCED RECTAL CANCER AND RESECTABILITY OF LIVER METASTASIS

With the development of magnetic resonance imaging (MRI), marginally resectable rectal cancer has been able to be delineated whether a patient presents high risk of having microscopically, or even macroscopically, unresected tumor without any preoperative treatment at initial diagnosis. LARC generally indicates rectal cancer with high T stage of ≥T3 or N + with or without circumferential margin (CRM) threatening and extramural vascular invasion. These are known as critical factors to achieve R0 resection and are associated with high recurrence rates; thus, patients presenting such features on MRI are regarded as good candidates for preoperative CRT.[9]

As for resectability of LM, indications for LM resection have evolved with advances in surgical techniques and CTx. Previously, large size and high number of LM and extensive bilobar distribution were important to decide resectability. However, according to the consensus of an international panel of multidisciplinary experts, the Expert Group on OncoSurgery management of Liver Metastases group reached in 2015, LM resection should not be denied to patients with adequate future liver remnant (FLR) and vascular inflow and outflow preservation after CTx.[10,11]

BRIEF REVIEWS ON THE TREATMENT GUIDELINES FOR LOCALLY ADVANCED RECTAL CANCER WITH SYNCHRONOUS LIVER METASTASIS

The recommendations of the LARC treatment guidelines differ from one another [Table 1]. In the National Comprehensive Cancer Network (NCCN) guideline version 3, two different treatment flowcharts are introduced according to the existence of preoperative systemic CTx for TanyNanyM1 resectable synchronous metastasis.[12] If a patient undergoes preoperative CRT first, surgical resection, followed by FOLFOX, CAPEOX, or 5-FU-based CTx is recommended. Meanwhile, if a patient receives upfront CTx with FOLFIRI, FOLFOX, or CAPEOX first for 2–3 months, either surgical resection with postoperative CRT or preoperative CRT with subsequent surgical resection, followed by postoperative CTx can follow the upfront CTx.[12] The French guideline declares that the treatment strategy for LARC should be chosen based on a case-by-case decision. For mid or low T3/T4 rectal cancer and/or node positivity, it recommends preoperative CTx for LM, followed by RT, or CRT. FOLFOX-based regimen is recommended for initially resectable LM, and intensified CTx with target agents is recommended for potentially resectable LM.[13] In the European Society for Medical Oncology guideline, perioperative CTx is recommended for colorectal cancer with synchronous LM, and FOLFOX and CAPOX are recommended as chemotherapeutic regimens.[14] In the second St. Gallen European Organisation for Research and Treatment of Cancer conference in 2016, a treatment strategy involving a systemic CTx with short course RT (SCRT) was favored by most of the panel. This was because 5-FU backbone CTx during preoperative CRT for LARC seems to result in undertreatment of LM for a long duration of conventionally fractionated CRT while SCRT

Table 1: National and international guidelines for locally advanced rectal cancer with synchronous liver metastasis

	Rectal cancer with synchronous resectable metastases
NCCN guideline[12]	Upfront CTx (doublet regimen: FOLFIRI, FOLFOX or CAPEOX) Followed by surgery (staged or simultaneous) and adjuvant CRT or Followed by 5-FU-based CRT (no recommendation of SCRT for T4 tumors) and surgery with subsequent CTx (same regimen as upfront CTx regimen) or 5-FU-based CRT (no recommendation of SCRT for T4 tumors), followed by surgery (staged or simultaneous) and subsequent adjuvant CTx (FOLFOX [preferred], CAPEOX [preferred], or 5-FU-based regimen [FL or capecitabine])
2016 French guidelines[13]	No standard management Upfront CTx, followed by RT or CRT for mid or low T3/T4 and/or N+: Regimen: FOFOX-based for initially resectable LM, adding a target agent for potentially resectable LM
ESMO[14]	Not specified for rectal cancer with LM Perioperative CTx is recommended for colorectal cancer with synchronous LM
Second St. Gallen EORTC conference in 2016[15]	Systemic CTx with SCRT and delayed surgery

LM: Liver metastasis, NCCN: National Comprehensive Cancer Network, CTx: Chemotherapy, CRT: Chemoradion therapy, SCRT: Short-course radiotherapy, ESMO: European Society for Medical Oncology, EORTC: European Organization for Research and Treatment of Cancer, 5-FU: 5-fluorouracil, RT: Radiation therapy, FL: 5-fluorouracil with leucovorin

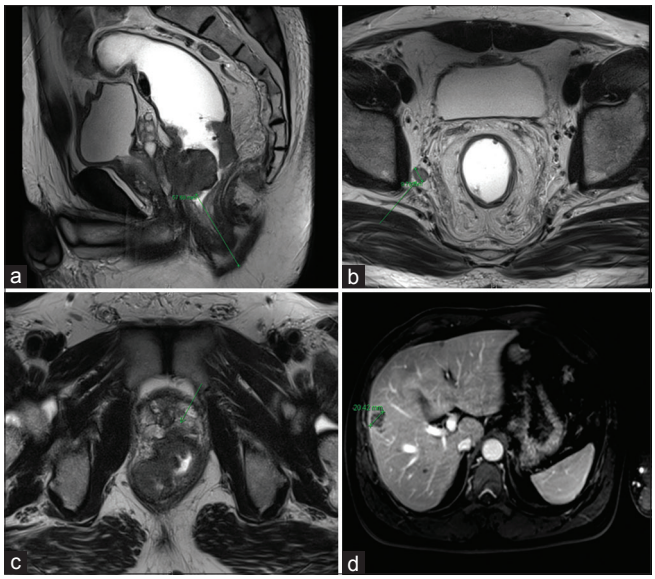

Figure 1: Pelvic magnetic resonance imaging and liver magnetic resonance imaging (a) sagittal view, showing low lying tumor, (b) right lateral pelvic node enlargement, (c) positive circumferential margin at 12 o'clock (d) synchronous solitary liver metastasis

with delayed surgery (4–8 weeks after completion of RT) can not only produce primary tumor regression but also allow early initiation of systemic CTx.[15]

ADMINISTRATION OF SYSTEMIC CHEMOTHERAPY VERSUS NO SYSTEMIC CHEMOTHERAPY BEFORE SURGICAL RESECTION FOR SYNCHRONOUS LIVER METASTASIS

LM is a main concern for LARC with synchronous LM; therefore, early administration of systemic CTx can be an option to prevent it.[7,16] There are a couple of possible strategies of preoperative systemic CTx according to the timing of administration. Induction CTx involves upfront CTx before preoperative CRT while consolidation CTx involves systemic CTx administered after CRT. Furthermore, systemic CTx can be administered before and after CRT as a sandwich protocol.

Even though several randomized trials have been established on the efficacy of perioperative CTx in resectable LM, most of them have included both metachronous and synchronous LM from either colon or rectal cancer.[17-19] Perioperative FOLFOX followed by liver resection has appeared to improve disease-free survival (DFS) without improvement of overall survival (OS) compared to surgery alone,[17] but the addition of epidermal growth factor receptor-targeting agent (cetuximab) to FOLFOX for perioperative CTx has shown detrimental results of shorter DFS.[18] A recent retrospective study, which has evaluated the efficacy of preoperative CTx in colorectal cancer with synchronous LM, has demonstrated that the 3-year DFS of the preoperative CTx group (preoperative CTx followed by primary tumor resection and postoperative CTx followed by liver resection) was longer than that of the primary resection first group (primary tumor resection followed by postoperative CTx and subsequent liver resection) (34.2% vs. 16.8%, $P = 0.019$).[6] However, rectal cancer has been presented in only 30% of the total population, and dose and timing of RT have not been clarified in the article. Meanwhile, data from the LiverMetSurvey registry, a prospective international registry of patients undergoing surgery for colorectal cancer with LM from 218 centers in 59 countries, have demonstrated similar 5-year OS between the preoperative CTx group (75/798, 42%) and the primary tumor resection first group (221/1554, 47%) within the patients with synchronous LM from colorectal cancer.[10]

Studies on the efficacy of preoperative CTx only in patients with LARC and synchronous resectable LM are very limited. A randomized trial that has evaluated preoperative CTx in those patients was reported by Cho *et al.*[8] This study showed similar R0 resection rate and local and systemic control in both preoperative CTx (preoperative CTx followed by CRT and surgery) and no preoperative CTx groups (preoperative CRT followed by surgery). As aforementioned, most studies on the efficacy of preoperative CTx were in the setting of both metachronous and synchronous LM from both colon and rectal cancers. Furthermore, even the study reported by Nordlinger *et al.*, which has been frequently cited as an evidence of benefit of preoperative CTx for LM from colorectal cancers, compared perioperative CTx, not preoperative CTx, to surgery alone; therefore, it remains unclear whether the benefit of DFS in the perioperative CTx group was owing to preoperative CTx, postoperative CTx, or both. A further prospective study on preoperative CTx for this disease category is needed to prove its oncologic benefit.

DILEMMA IN DETERMINING TIMING AND SEQUENCE OF PREOPERATIVE TREATMENT MODALITIES

To achieve curative resection for both primary LARC and synchronous LM, several factors should be considered, such as time duration between CRT and surgery, chemotherapeutic regimen, surgeon's competency for primary tumor and number of cycles of preoperative systemic CTx, toxicity of chemotherapeutic agents for LM, and tumor biology for both. If treatment focus is weighed on one site over the other, it might lead to either progression of primary tumor or LM beyond resectability.

To deal with this dilemma, several treatment strategies have been introduced in the literature.[20]

UPFRONT CHEMOTHERAPY FOLLOWED BY SHORT-COURSE RADIOTHERAPY AND DELAYED SURGERY

The German CAO/ARO/AIO-94 trial has demonstrated that preoperative CRT followed by TME had 6% of 5-year local recurrence (LR) rate with lower toxicity rate compared to postoperative CRT.[21-23] Based on this result, 5-FU based conventionally fractionated (1.8 Gy × 28 fractions) preoperative CRT has been established as a standard treatment for patients with nonmetastatic LARC. However, when it comes to LARC with synchronous LM, delay of administration of systemic therapy has become a great concern due to the potential progression of LM beyond resectability during preoperative conventionally fractionated CRT. Chemotherapeutic agents, conventionally used for CRT, are 5-FU-based regimens, which are used as a radiosensitizer in nature.[16] Thus, the administration of chemotherapeutic agents as part of CRT is suboptimal to have an impact on systemic control.

Accordingly, a rising need for early administration of preoperative systemic CTx and shortened duration of RT is not surprising for metastatic condition. In that sense, clinical values of upfront CTx with SCRT have been evaluated in our institution. At first, a case series of six patients with LARC with synchronous and potentially resectable distant metastases was reported in 2011.[4] In all patients, 4–6 cycles of FOLFOX (5-FU with leucovorin and oxaliplatin) regimen with or without a target agent (cetuximab or bevacizumab) were administered, and SCRT (5 Gy × 5 fractions) followed upfront CTx. Simultaneous resections for both sites were performed after the evaluation of tumor response at least 6 weeks after completion of SCRT. During the waiting period to allow tumor regression, additional 2–5 cycles of the same regimen as the upfront CTx were administered. As a result, R0 resection was achieved, except in one patient for primary tumor; another patient developed distant recurrence during the median follow-up of 16.7 months. LR or mortality was not observed with acceptable adverse events.

Further, retrospective analysis of 50 patients with LARC and synchronous distant metastases has been performed.[5] All the patients received preoperative treatment schedule with the same protocol as the aforementioned case series, but either FOLFOX or FOLFIRI was used as a chemotherapeutic regimen with or without a target agent. Among the 50 patients, 35 (70%) underwent resection for both sites, and 30 achieved R0. However, 7 patients (14%) showed progression of LM beyond resectability and 2 refused curative resection. The remaining 6 patients (12%) demonstrated clinical complete response on imaging tests; therefore, 44 patients (88%) received resection for primary surgery. Among those 44 patients, anastomosis leak developed in 7 (16%), with minor leak in 4 of them. The pathologic complete response (ypCR) rate was 13.6%, and the 2-year progression-free survival (PFS) rate was 34.8%. This retrospective analysis showed that the upfront chemotherapy with SCRT followed by delayed surgery could be a feasible and tolerable treatment option for LARC with distant metastases.

Thereafter, a phase II single-arm study for LARC with synchronous liver-only metastasis has been conducted.[7] The eligibility of this study was focused on LARC (cT4 or cT3 with <2 mm of CRM on MRI) with synchronous liver-only metastases (no number or size limitation of LM), and the treatment protocol consisted of 4 cycles of preoperative FOLFOX followed by SCRT and subsequent 4 cycles of FOLFOX followed by simultaneous resection for primary tumor and LM. Among 32 patients, surgical resection has been performed in 25 patients (78%), and an R0 resection rate of 63% for both sites has been observed. A median OS and PFS of 38 and 9 months, respectively, and a tumor downstaging rate of 54% was found. Interestingly, R0 resection was achieved in all the patients who decided to have resectability on response evaluation for LM by the multidisciplinary team (MDT). However, 5 patients with cT4 showed no invasion to adjacent organs on MRI performed for response evaluation, but they presented positive CRM in the final pathologic reports. Therefore, application of SCRT with upfront CTx to patients with cT4 in this disease category should be carefully considered through MDT approach due to the relatively high chance of R0 resection failure. This is consistent with the NCCN guideline that does not recommend SCRT for T4 tumors of LARC with synchronous resectable LM. Regarding the 3 patients who were not eligible for the resection of LM, they all presented with over 4 lesions of LM and disease progression of LM during the preoperative treatment period. In that sense, the application of preoperative treatment has a risk of LM progression; thereby, liver-first approach or upfront hepatectomy may be an alternative treatment option for some selected patients with synchronous resectable LM, and those strategies will be discussed later. For safety profile, 4 of 32 patients (17%) developed anastomosis leak and underwent second operation, which is comparable with the previous report on SCRT followed by delayed surgery (safety range, 8%–21%).[24-27] This study has shown

that this strategy can be an acceptable option for treatment of LARC with synchronous LM.

SHORT-COURSE RADIOTHERAPY WITH SUBSEQUENT SYSTEMIC CHEMOTHERAPY FOLLOWED BY DELAYED SURGERY

Recently, van Dijk *et al.* established a single-arm phase II study to evaluate the efficacy of SCRT followed by 6 cycles of capecitabine, oxaliplatin, and bevacizumab (CapeOx-bev) with delayed surgery, 6–8 weeks after the last use of bevacizumab for rectal cancer with synchronous systemic metastases.[25] The patients with resectable LM with ≤6 lesions or lung metastases were included, and the most commonly observed clinical scenario was cT3N1-2 with LM among 50 patients. Forty-eight (96%) patients could undergo scheduled surgery (simultaneous or staged), and R0 rates of primary tumor and both primary and metastases were 90% and 72%, respectively. The ypCR rate of the primary tumor was 26%, and the 2-year OS and DFS was 80% and 64%, respectively. Most recurrences occurred in the liver, and LR occurred only in two patients. For the safety aspect of this strategy, adverse effects of preoperative SCRT followed by CapeOx-bev were comparable with the previous report on the same regimen.[28] The most common postoperative morbidity was infection-related event (25%), mostly wound infection or abdominal cavity abscess, which were comparable with previous reports on postoperative complications in bevacizumab-used cases although more frequent surgical interventions for the complications were needed.[28-31] Only one anastomosis leak, one rectal stump leak, and no postoperative mortality were observed. This study showed that the intensification of chemoregimen with additional target therapy might be a feasible and potentially curable treatment option for patients with LARC with synchronous LM demonstrating comparable local control compared to the previous conventionally fractionated LCRT.[32]

SYSTEMIC CHEMOTHERAPY WITH INTENSIFIED CHEMOREGIMEN IN THE SETTING OF LONG-COURSE CHEMORADIATION THERAPY

To overcome the drawback of the possibility of disease progression during LCRT in patients with synchronous LM, early use of systemic CTx with intensified chemo regimen for LCRT has also been investigated. Recently, Cho *et al.* conducted a phase II trial to examine the efficacy of induction CapeOx for LARC (cT3/T4 or N positivity) with synchronous resectable LM (≤5, no invasion of major vessels, considered resectable by MDT and adequate FLR).[8] Two randomly assigned arms, CapeOx followed by CapeOx-RT (50.4 Gy) and surgery (arm A, 18 patients) versus CapeOx-RT (50.4 Gy) followed by surgery (arm B, 20 patients), were compared. R0 rates for both sites were 77.8% in arm A and 70% in arm B. The rate of ypCR was 11.1% and 5.0%, and the median PFS was 14.2 and 15.1 months, respectively. The 3-year OS and PFS rates were 75% and 25.1% versus 88.8% and 36.3%, respectively. Statistical analyses demonstrated no significant differences. Recurrence rates were over 50% for both arms, and the most common recurrence pattern was distant recurrence. LR was not found in arm A and was found in two patients in arm B. Although satisfactory local control from preoperative CRT was achieved, systemic control was not satisfactory. Therefore, more stress should be on improving systemic control, and more suitable strategies should be explored in the future.

A phase II trial evaluating feasibility of a novel regimen has been established. This study has included a 12-week course of treatment with split-course Ox-5FU + RT (50.4 Gy), alternating with FOLFOX in patients with symptomatic LARC with synchronous systemic metastases.[33] FDG-PET metabolic response rates for primary and metastatic lesion have been observed to be 96% and 60%, respectively, with a completion rate of planned treatment of 92%; however, survival outcome or recurrence pattern is not available.

LIVER-FIRST APPROACH AND UPFRONT HEPATECTOMY

LARC with synchronous LM has been mostly traditionally treated with preoperative CRT followed by staged resection of primary tumor and LM. In addition to this primary-first approach, liver-first approach was first described in 2006, in an effort to overcome progression of LM beyond resectability during CRT and postoperative care.[34] The liver-first approach comprises upfront CTx followed by liver resection and subsequent CRT and primary tumor resection. The theoretical base of this approach is that prognosis of patients with LM may be more dependent on LM rather than the primary lesion. Possible benefits of the liver-first approach are early use of systemic CTx, minimization of progression of LM, and *in vivo* evaluation of responsiveness of preoperative upfront systemic CTx. Many studies have evaluated its efficacy compared to the primary-first approach, and many of them have reported the liver-first approach as favored; however, most of them have analyzed the primary–first cases before 2000, which could lead to bias due to improved efficacy of recent chemotherapeutic agents.[16,35,36] In 2012, the LiverMetSurvey registry-based study established by Andrea *et al.* reported that the 5-year OS and DFS were 42% and 30% in the liver-first approach, and 55% and 29% in the

primary-first approach, respectively, with no statistical difference.[35] However, the patients who were included in the analysis completed their planned treatment pathway in both groups. Considering the high completion rate, largely up to 80%, the liver-first approach may have advantage over approximately 30% of the completion rate observed in the primary-first approach.[16,35-41] Meanwhile, this study showed similar compliance rate when compared with the 78% of resection rate for both sites reported by Kim *et al.* in patients treated with upfront CTx with SCRT followed by delayed simultaneous resection.[7]

Liver-first approach, however, presents a possibility of complications development induced by progression of the primary tumor, such as bleeding, obstruction, and perforation; this is relatively rare though.[3,42] Further delay in the resection of primary tumor can also occur in case of severe postoperative complication after liver resection. Another disadvantage is the possibility of disappearance of LM on images owing to good response, which, however, does not indicate pCR. Approximately 38%–74% have been reported to develop LR after disappearance of LM on imaging studies[43,44] CTx-induced liver injury, such as hepatic steatosis and sinusoidal obstruction, is also a drawback of this approach, resulting in increased postoperative morbidity.[36,45] However, based on the previous reports, rates of posthepatectomy complications are comparable, ranging from 16% to 39%, with mostly minor complications in the liver-first strategy for synchronous LM from colon and rectal cancer.[34,39,40,46-48] Verhoef *et al.* reported surgical outcomes and long-term outcomes of the liver-first approach for 42 patients with LARC with synchronous LM.[47] This study reported that 74% of the patients completed the planned treatment, with a 5-year OS of 67%; this approach also contributed in the prevention of unnecessary primary tumor resection for the patients who developed unresectable LM during preoperative CTx. Postoperative complication was observed in 22.5% patients; however, they were all minor complications of Clavien-Dindo classification I or II, except one patient with IIIa.

To avoid aforementioned drawbacks of upfront CTx in the liver-first approach, such as CTx-induced liver injury and missing lesions, upfront hepatectomy strategy has been proposed. This strategy comprises resection of LM followed by systemic CTx and/or CRT and subsequent resection of primary tumor and adjuvant CTx.[49] Without preoperative systemic CTx, CTx-induced liver injury can be avoided; in this way, the risk of postoperative complications caused by impaired liver function can be reduced, along with hematologic and mucocutaneous complications induced by the systemic effect of CTx. Furthermore, missing lesions of LM during preoperative treatment before liver resection have been reported in up to 36% of cases, and recurrence rates of the missing lesions after disappearance have been reported in 38%–74% of cases.[41,43,44] In addition, progression of LM beyond resectability has been reported in 7%–37%.[16,50] Even though there have been no reports on clinical outcomes for this strategy, considering these cases, upfront hepatectomy without preoperative CTx may highly benefit selected patients with clearly resectable LM.[16]

CRITICAL ROLE OF MULTIDISCIPLINARY TEAM AND FUTURE PERSPECTIVES

As reviewed, there are various combinations of multimodal treatments for LARC with synchronous LM. In this article, advantages and disadvantages of possible treatment strategies for LARC with synchronous resectable LM by some previous articles are discussed. The initial step for treating this condition is to determine resectability of primary tumor and LM. Determination of resectability is a complex process; thus, MDT approach can be beneficial in increasing the accuracy of decision-making and determining the most suitable treatment strategies for each individual along with patients' satisfactory and educational benefit.

In spite of advances in metastatic rectal cancer treatment due to the development of chemotherapeutic agents and local treatment modalities, surgical resection for both primary and metastatic lesions is the only curable treatment. According to two key determinants, timing and sequencing of surgeries and preoperative treatments, previous studies have suggested different treatment strategies for this disease category. However, the studies on LARC with synchronous LM are very limited, and only a few of them are randomized controlled trials (RCT). The strategies mentioned here have been all suggested in an effort to increase rate of R0 for both primary tumor and metastases. None of the options have been proven to be the best-treatment strategies, and there are limited studies and evidences to draw any conclusion. Further, RCTs to evaluate oncologic outcomes and preoperative treatment-related and surgery-related complications of suggested strategies should be performed. Therefore, it is essential to decide the most suitable strategy for each patient with LARC with synchronous LM through an MDT approach to avoid detrimental complications from unnecessary treatment procedures and delay of systemic CTx or other critical interventions.

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Conflicts of interest

There are no conflicts of interest.

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